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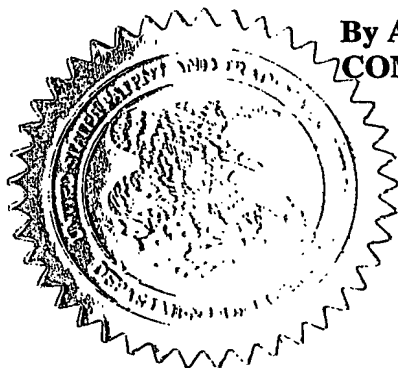
February 19, 2004

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APPLICATION NUMBER: 60/431,937

FILING DATE: December 09, 2002

RELATED PCT APPLICATION NUMBER: PCT/US03/39196



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12/09/02

1135 U.S. PTO

BUREAU OF PATENTS

12-10-02

APPROV

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PTO/SB/16 (12-97)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

11002 U.S. PTO
 60/431937
 12/09/02

INVENTOR(S)					
Given Name (first and middle [if any])		Family Name or Surname		Residence (City and either State or Foreign Country)	
David Gilia Paul		Felfel Mendez Shilling		La Jolla, CA San Diego, CA San Diego, CA	
<input type="checkbox"/> Additional Inventors are being named on the _____ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (280 characters max)					
Method of Inhibiting Neural Transmission Mediated by Serotonin and Enhancing Sensorimotor Gating					
CORRESPONDENCE ADDRESS					
Direct all correspondence to:			<input type="checkbox"/> Customer Number <input type="text"/> → <input type="text"/> Place Customer Number Bar Code Label here		
OR					
<input checked="" type="checkbox"/> Firm or Individual Name		FUESS & DAVIDENAS			
Address		17258 Amarillo Road			
Address					
City	Ramona	State	CA	ZIP	92065
Country	USA	Telephone	(760) 788-7401	Fax	(760) 788-5846
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/>	Specification Number of Pages	19	<input type="checkbox"/>	Small Entity Statement	
<input checked="" type="checkbox"/>	Drawing(s) Number of Sheets	2	<input type="checkbox"/>	Other (specify) <input type="text"/>	
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)					
<input checked="" type="checkbox"/>	A check or money order is enclosed to cover the filing fees				FILING FEE AMOUNT (\$)
<input checked="" type="checkbox"/>	The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: <input type="text"/>				\$80.00
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government					
<input checked="" type="checkbox"/> No					
<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are _____					

Respectfully submitted, William C. Fuess
 SIGNATURE
 TYPED or PRINTED NAME William C. Fuess
 TELEPHONE (760) 788-7401

Date 12/09/02

REGISTRATION NO. 30,054
 (if appropriate)
 Docket Number: SD 2003-090

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO Box Provisional Application, Assistant Commissioner for Patents, Washington, DC 20231

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FEE TRANSMITTAL

Patent fees are subject to annual revision on October 1.
These are the fees effective October 1, 1997.
Small Entity payments must be supported by a small entity statement,
otherwise large entity fees must be paid. See Forms PTO/SB/09-12
See 37 C.F.R. §§ 1.27 and 1.28

TOTAL AMOUNT OF PAYMENT (\$) 80.00

Complete if Known

Application Number
Filing Date 12/09/02
First Named Inventor David Feifel
Examiner Name
Group / Art Unit
Attorney Docket No. SD 2003-090

METHOD OF PAYMENT (check one)

1. ☐ The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:
Deposit Account Number
Deposit Account Name
☐ Charge Any Additional Fee Required Under 37 C.F.R. §§ 1.16 and 1.17 ☐ Charge the Issue Fee Set in 37 C.F.R. § 1.18 at the Mailing of the Notice of Allowance

2. ☒ Payment Enclosed:
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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Code (\$)	Small Entity Code (\$)	Fee Description	Fee Paid
101 790	201 395	Utility filing fee	
106 330	206 165	Design filing fee	
107 540	207 270	Plant filing fee	
108 790	208 395	Reissue filing fee	80.00
114 150	214 75	Provisional filing fee	
SUBTOTAL (1)			80.00

2. EXTRA CLAIM FEES

Total Claims	Extra Claims	Fee from below	Fee Paid
Independent	-20** =	X	
Multiple Dependent	-3** =	X	

**or number previously paid, if greater, For Reissues, see below

Large Entity Code (\$)	Small Entity Code (\$)	Fee Description
103 22	203 11	Claims in excess of 20
102 82	202 41	Independent claims in excess of 3
104 270	204 135	Multiple dependent claim, if not paid
109 82	209 41	** Reissue independent claims over original patent
110 22	210 11	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$) 0

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Code (\$)	Small Entity Code (\$)	Fee Description	Fee Paid
105 130	205 65	Surcharge - late filing fee or oath	
127 50	227 25	Surcharge - late provisional filing fee or cover sheet	
139 130	139 130	Non-English specification	
147 2,520	147 2,520	For filing a request for reexamination	
112 920*	112 920*	Requesting publication of SIR prior to Examiner action	
113 1,840*	113 1,840*	Requesting publication of SIR after Examiner action	
115 110	215 55	Extension for reply within first month	
116 400	216 200	Extension for reply within second month	
117 950	217 475	Extension for reply within third month	
118 1,510	218 755	Extension for reply within fourth month	
128 2,060	228 1,030	Extension for reply within fifth month	
119 310	219 155	Notice of Appeal	
120 310	220 155	Filing a brief in support of an appeal	
121 270	221 135	Request for oral hearing	
138 1,510	138 1,510	Petition to institute a public use proceeding	
140 110	240 55	Petition to revive - unavoidable	
141 1,320	241 660	Petition to revive - unintentional	
142 1,320	242 660	Utility issue fee (or reissue)	
143 450	243 225	Design issue fee	
144 670	244 335	Plant issue fee	
122 130	122 130	Petitions to the Commissioner	
123 50	123 50	Petitions related to provisional applications	
126 240	126 240	Submission of Information Disclosure Stmt	
581 40	581 40	Recording each patent assignment per property (times number of properties)	
146 790	246 395	Filing a submission after final rejection (37 CFR 1.129(a))	
149 790	249 395	For each additional invention to be examined (37 CFR 1.129(b))	

Other fee (specify) _____

Other fee (specify) _____

SUBTOTAL (3) (\$) 0

* Reduced by Basic Filing Fee Paid

SUBMITTED BY

Typed or Printed Name William C. Fuess

Signature *William C. Fuess*

Date 12/09/02

Complete (if applicable)

Reg. Number 30,054

Deposit Account User ID

Burden Hour Statement. This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO Assistant Commissioner for Patents, Washington, DC 20231.

Brought in by: LSPROPRIETARY INFORMATIONCASE No. 2003-090**TECHNOLOGY TRANSFER and INTELLECTUAL PROPERTY SERVICES, UCSD
INVENTION AND TECHNOLOGY DISCLOSURE FORM****A. TITLE OF INVENTION**

Create a short title describing the general nature of the invention without revealing the specific details that would enable others to reproduce the invention (e.g., new anticancer compound, method for chip fabrication, etc.) Please limit the title to 60 characters

Method of inhibiting neural transmission mediated by serotonin-2A and enhancing sensorimotor gating.

B. UCSD INVENTOR(S)

List all UCSD employees or students who intellectually contributed to the invention. Please also indicate any joint or special appointment with non-UCSD institutions (e.g., VA and HHMI) in the "Position" box.

Name: David Feifel	S. <u> </u>	Position: Assoc. Professor In Residence Joint or Non-UCSD Affiliation:
Dept.: Psychiatry Mail Code: MC8218	Work Address: 200 West Arbor Drive San Diego, CA 92130-8218	
Wk. Phone: (619) 543-2485	Fax: (619) 543-3738	Email: dfeifel@ucsd.edu
Hm. Address: 8241 La Jolla Scenic Drive North La Jolla, CA 92037		Hm. Phone (858) 558-6113

Name: Gilia Mendez	SS#: <u> </u>	Position: Lab Assistant Joint or Non-UCSD Affiliation:
Dept.: Mail Code:	Wk. Address:	
Wk. Phone:	Fax:	Email:
Hm. Address:		Hm. Phone:

Name: Paul Shilling	SS#: <u> </u>	Position: Post-Doc Fellow Joint or Non-UCSD Affiliation:
Dept.: Mail Code:	Wk. Address:	
Wk. Phone:	Fax:	Email:

C. INVENTORS NOT AFFILIATED WITH UCSD

If an inventor is not a UCSD employee or student, please provide information below

Name:	Position: Chemist	Nature of employment:
Employer:	Wk. Address:	
Wk. Phone:	Fax:	Email:
Nature of Contribution (please provide information explaining why this person is a co-inventor)		

Name:	Position:	Nature of employment:
Employer:	Wk. Address:	
Wk. Phone:	Fax:	Email:
Nature of Contribution (please provide information explaining why this person is a co-inventor):		

Please attach a separate page for additional non-UCSD inventors

D. FUNDING SOURCES FOR THE PROJECT UNDER WHICH THE INVENTION WAS MADE

As funding often carries obligations to a sponsor, be sure to include all outside agencies, organizations, or companies that provided any funding to any inventor for the research that led to the conception or first actual reduction to practice of the invention. Please include any companies that have supplied materials in exchange for intellectual property rights.

SPONSORS	GRANT NUMBER	PRINCIPAL INVESTIGATOR
National Alliance Research and Schizophrenia		David Feifel
NIH	MH6245-01 Also Supplied compound for inventive studies	David Feifel
Parke Davis	Supplied Compound for initial study	

Is there any other corporate relationship that we should be aware of concerning this invention? Y N

Name of Company: _____ ParkeDavis _____

Please explain the nature of the relationship: _____ Synthesized and patented compound _____

E. MATERIAL TRANSFER AGREEMENT (MTA)

Please list and attach copies, if available, of any Material Transfer Agreement or any other written or oral agreement used to obtain any material used for this invention.

An MTA was possibly executed with Parke Davis to obtain the original sample of PD149163 to do initial studies resulting in one publication (Feifel et al, 1999, Journal of Pharmaceuticals and Experimental Therapeutics). Parke Davis stopped producing this compound. Subsequently I have obtained compound from SRI International, Menlo Park, CA free of charge (underwritten by NIH chemical synthesis program).

F. DESCRIPTION OF EVENTS:

This information is important for deciding priority of invention and/or legal "bars" to patenting. In general, publications, in any medium, before the date a formal patent application is filed in a national patent office can cause a bar to patent filing in most foreign countries. While United States patent law allows inventors up to one year to file a patent application after the first publication, public use, or sale, the loss of foreign rights is often very important to potential industrial licensees. **SEE APPENDED SECTION BELOW**

EVENTS	DATE	INDICATE THE WRITTEN RECORD (e.g., notebook, letter, email). IF ORAL DISCLOSURE, INDICATE TO WHOM.
1. Initial conception of the idea		
2. First description of complete invention, oral or written		
3. First successful demonstration (first actual reduction to practice)		
4. Has this work been. i. submitted for publication? Y N ii. accepted for publication? Y N iii. Published? Y N		
5. Have you presented this work at a conference or meeting? i. Did you submit an abstract? Y N ii. Was abstract published? Y N iii. Name of conference or meeting? Y N i. Did presentation include handouts? Y N		

G. INVENTORS' SIGNATURES

By signature below, I acknowledge my responsibilities and rights to royalty-sharing under the current University of California Patent Policy.

David Feifel
Inventor signature

12/3/02
Date

Inventor signature

Date

H. WITNESS - invention disclosed to and understood by:

Larry Brand
Witness signature

12-3-02
Date

LARRY BRAND
Print witness name

I. ABOUT THE INVENTION

Please write a summary of the invention following the numbered guidelines listed below. Since this information will be used to determine patentability, commercial uses, and potential licensees of the invention, please provide as many details as possible. If you have a written manuscript descriptive of your invention, please also attach a copy to this form.

1. What exactly does your invention do?

My invention is that neurotensin peptide mimetics modified to enter the CNS (PD149163) do the following:

Reverses sensorimotor gating deficits (as measured by prepulse inhibition of startle reflex) in Brattleboro Rat, a commercial rat with a single gene deficit which I discovered to have innate abnormalities in prepulse inhibition similar to humans with neuropsychiatric disorders (i.e. schizophrenia, Huntington's disease, bipolar disorder). This effect is likely predictive of therapeutic effects in neuropsychiatric disorders.

Also improves sensorimotor gating in normal rats.

Also reverses deficits in sensorimotor gating deficits produced by drugs that are serotonin-2 agonists and alpha-1 agonists (previous pharmacological effects not attributed to neurotensin or neurotensin drugs).

2. What is unique, novel, or better about your invention as compared to existing art?

PD149163 appears to be more potent and longer lasting than other psychotropic drugs tested in preclinical tests. It performed better than current "gold standard" antipsychotic drugs and evidence of effects lasted several days after a single administration which is not seen with currently existing psychotropic drugs.

Compared to existing psychotropic medication:

- Appears to have unique mechanism of action (i.e. modulates relevant CNS circuits implicated in neuropsychiatric conditions and normal sensorimotor gating without directly bind to the either monoamine, GABA, glutamate or acetylcholine receptors (the therapeutic mechanism attributed to all current psychotropic medication).

- appears to have a favorable side effect profile based upon preclinical tests

- Appears to have longer duration of effects from single administration of other psychotropic drugs tested

- Compared to existing art regarding this category of compound (neurotensin agonist), it appears to have previously unknown mechanisms and effects that I discovered (i.e. antagonism of serotonin-2A and alpha 1-adrenergic functions and facilitation of sensorimotor gating in animals with genetically induced deficient sensorimotor gating and in normal animals). Furthermore neurotensin analogs

3. What is the existing art to which you are comparing?

1. Antipsychotic drugs
2. Antidepressant Drugs
3. Neurotensin mimetics (e.g. what is currently known about this same compound, and family and other neur that enter the CNS e.g NT69L)

4. Describe how your invention works (or may work). Please include drawings, schematics, figures, etc., necessary to explain how the invention works or may work

Mechanism is not fully elucidated.

However, in preclinical predictive test of potential psychotropic (especially antipsychotic) usefulness a representative compound of this family (PD149163) was able to reverse startle abnormalities (sensorimotor gating, prepulse inhibition) in genetically mutant rats more effectively than some of the best available antipsychotics. It was also able to improve startle parameters in normal rats. Therefore it appears to modulate sensorimotor gating circuits.

In other preclinical tests done in my laboratory aimed at elucidating mechanism, it appeared to reverse CNS effects of a serotonin 5HT_{2A} and alpha-1 adrenergic agonists, suggesting inhibition of neurotransmission mediated by these receptors. (Previously inhibition of dopamine receptor mediated neurotransmission was the only therapeutic mechanism associated with this family of compounds)

5. Describe the stage of development of the invention (e.g., concept stage, experimental data stage, computer model simulation stage, working prototype stage, etc.). Please include data, photographs, etc., indicating the stages of development.

Preclinical Stage.

Test in my laboratory using animal tests predictive of psychotropic efficacy. Some of these predictive tests have been established in the field, others I have innovated.

6. What are potential commercial applications of your invention?

Drugs that target neurotensin receptors that may have therapeutic effects for neuropsychiatric disorders: Including schizophrenia, schizoaffective disorder, bipolar disorder, depression, anxiety disorders, autism, Huntingtons disease, obsessive-compulsive disorders.

May also have prophylactic efficacy for people at high risk for these conditions.

May also act as an extended duration therapy for neuropsychiatric disorders

May work more rapidly than current drugs which all have a delayed effect (faster effect in preclinical studies)

May augment the effects of current psychotropic drugs when used in combination.

May also improve cognitive performance in people who do not have neuropsychiatric disorders

J. COMPANIES

Based on your knowledge, please provide the names and addresses of companies that are, or may be, interested in manufacturing, using, and/or further developing your invention.

Company & Contact Name	Company Address
Roche, Janssen, Eli Lilly, Pfizer, Bristol Myers Squibb, AstraZeneca, Pharmacy and Upjohn, Parke-Davis	
Neurocrine, Solvay, Abbot Laboratories	

1. Please list or attach any literature references that most closely describe the state of the related art before your invention. If possible, please consider doing a search of the literature, because it will help in the evaluation of your invention.

U.S. Patent # 5,393, 740 "Neurotensin Hexapeptides" (02-28-95)
 U.S. Patent # 5,407, 916 "Neurotensin Mimetics as Central Nervous System Agents" (04-18-1995)
 Kinkead B. et al "Neurotensin: an endogenous Antipsychotic? Curr Opin Pharmacol, 2002 Feb; 2(1):99-103
 Feifel et al, 1999 "Novel Antipsychotic-Like Effects On Prepulse Inhibition of Startle Produced By A Neurotensin Agonist. (Appended)
 Feifel et al., (In Press) A systemically administered neurotensin agonist blocks disruption of prepulse inhibition produced by a serotonin-2A agonist. (Appended).
 Feifel et al, 2002 (Abstract of poster to be presented at ACNP meeting, December 9, 2002) EVIDENCE THAT NON-DOPAMINE MECHANISMS CONTRIBUTE TO THE ANTIPSYCHOTIC-LIKE EFFECTS OF NEUROTENSIN AGONISTS (Appended)

2. If a company is interested in licensing your invention, would you be interested in assisting or working with the company to develop your invention into a product under a sponsored or research agreement with the University? Y / N

YES

I would also seriously consider establishing a company to acquire license and further develop invention.

Events relevant to invention:

Preclinical work suggest that neurotensin, an endogenous neuropeptide that has 13 amino acids may have use as an antipsychotic based upon the fact that it inhibits effects of dopamine in brain. - Series of studies, multiple investigators beginning in 1980s

Parke Davis reports new family of compounds that are active fragment of neurotensin NT(8-13) chemically modified to increase stability and cross into the CNS after systemic injection (Wustrow et al, 1995) Patent filed 1995 ("Neurotensin Mimetics as central Nervous System Agents), suggesting these compounds may be effective for schizophrenia or analgesia

I collaborate with Parke-Davis investigators who supply me with an amount of one of the neurotensin mimetics (PD149163) to test it in startle-based animal screen for antipsychotic mechanisms. Results show equivocal effects of dopamine (previously implicated basis for antipsychosis) but indirect evidence for non-dopamine mechanisms of antipsychosis (reversal of the effects of glutamate antagonist). Results published in 1999 (Feifel et al, 1999)

I begin further studies on PD149163 based upon interesting results of 1999 paper. Parke Davis stopped producing compound. Therefore I have since obtained compound free of charge from SRI International which is commissioned by NIH (chemical synthesis program) to synthesis this for research purposes.

Recent studies in my lab show PD149163 reverses disruption of prepulse inhibition (a measure of sensorimotor gating) produced by a serotonin-2A receptor agonist (DOI). This suggest PD149163 (and presumably others neurotensin mimetics in this family) can antagonize the brain pathways mediated by serotonin-2A receptors. This is an important pharmacological mechanism shared by many new generation psychotropics that are useful to treat psychosis, depression, mania, anxiety Those drugs do so by directly binding serotonin-2A receptors (Neurotensin mimetics do not) This study was performed January, 2001 This finding has been accepted for publication in the journal Neuropsychopharmacology and the MS form has been placed upon their website since November, 2002 (But not formally published in print as a final document). (See attached manuscript, Feifel, Mendez and Shilling).

Recent studies in my lab with another NT69L, another NT(8-13) mimetic stabilized to enter the CNS by another chemical means (obtained by a colleague who synthesized it a Mayo in Jacksonville, Florida) did not show the ability to reverse effects of DOI (unpublished finding) Therefore, this pharmacological property may be unique to PD14916 or chemically related neurotensin mimetics (stabilized by an amide bond)

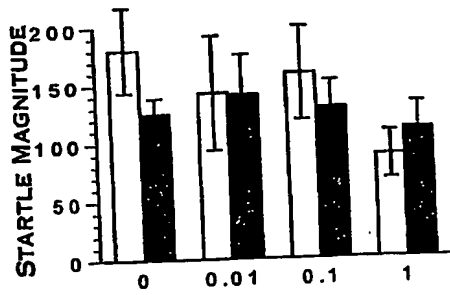
Recently a study in my lab showed that PD149163 reverses disruption of prepulse inhibition (a measure of sensorimotor gating) produced by an alpha-1 adrenergic receptor agonist (cirazoline). This suggest PD149163 (and presumably others neurotensin mimetics in this family) can antagonize the brain pathways mediated by alpha-1 adrenergic receptors. This is an important pharmacological mechanism of of many new generation antipsychotics are thought to contribute to their antipsychotic effects (although less established than serotonin-2A inhibition). Study done in October, 2002 (unpublished).

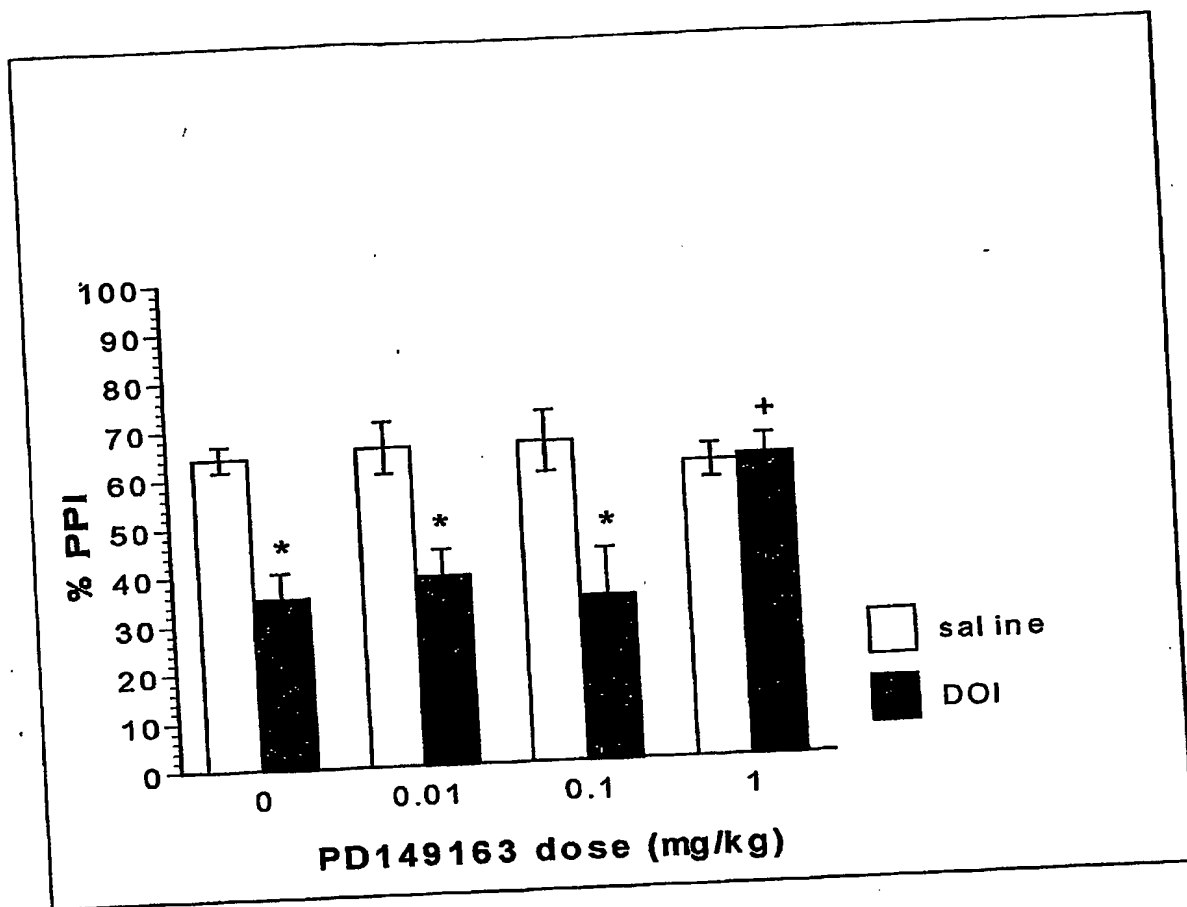
I recently discovered that well known a genetically mutated rat (Brattleboro Rat) has a deficits in sensorimotor gating (measured as prepulse inhibition of startle response) similar to patients with some neuropsychiatric disorders. Reversal of this abnormality is likely a marker for psychotropic drugs (especially antipsychotics)

Acute administration of PD149163 reverses this abnormality in Brattleboro rats but standard antipsychotic drugs did not. Furthermore, PD149163 did increased baseline sensorimotor gating in normal rats. Critical study conducted August, 2002 (unpublished but this data will be presented at the American College of Neuropharmacology meeting on December 9, 2003 as a poster)

All these things suggest that Neurotensin agonists (or at least PD149163 and chemically related drugs) and psychotropic uses and mechanisms not previously taught by the existing art

Please send completed forms and supporting materials to.





**A SYSTEMICALLY ADMINISTERED NEUROTENSIN AGONIST BLOCKS
DISRUPTION OF PREPULSE INHIBITION PRODUCED BY A SEROTONIN-2A
AGONIST**

David Feifel, M.D., Ph.D.*, Gilia Melendez, M.S., Paul D. Shilling, Ph.D.

Department of Psychiatry, University of California, San Diego

San Diego, California

BRIEF REPORT

(Accepted for Publication. Manuscript available on Publishers website)

Correspondence to:

David Feifel, M.D., Ph.D
Department of Psychiatry
UCSD Medical Center
200 West Arbor Drive
San Diego, CA 92103-8218
Tel: (619)543-2485
FAX: (619)543-3738
E-mail: dfeifel@ucsd.edu

ABSTRACT

Prepulse inhibition (PPI) of the startle reflex can be disrupted by drugs that act as agonists at the serotonin (5HT) 2A receptor, such as DOI, and this effect is blocked by drugs that inhibit 5-HT_{2A} transmission. We tested the effects of systemic administration of PD149163, a neurotensin agonist, on DOI-induced disruption of PPI in Sprague-Dawley rats. PD149163 completely and dose-dependently blocked the PPI deficits produced by DOI. These findings suggest that, in addition to their established ability to inhibit dopamine transmission, neurotensin agonists may also inhibit 5-HT_{2A} transmission, a pharmacological feature associated with atypical antipsychotic drugs.

INTRODUCTION

Prepulse inhibition of the acoustic startle reflex (PPI) is the reduction in the startle response when the startle-eliciting stimulus is immediately preceded by a weak stimulus. PPI, an operational measure of sensorimotor gating, is deficient in schizophrenia patients (Geyer et al., 2001).

Deficits in PPI can be produced in rats by a number of pharmacologically distinct "psychotomimetic" compounds (Geyer, Krebs-Thomson et al., 2001 for review). typical and atypical antipsychotics reverse PPI deficits produced by

dopamine agonists such as amphetamine and apomorphine. The mechanism implicated has been blockade of dopamine-2 (D2) receptors. In contrast, PPI disruption produced by non-competitive NMDA antagonists such as phencyclidine (PCP) or dizocilpine is antagonized by atypical but not typical antipsychotics and blockade of serotonin (5-HT) 2A and/or alpha-1 noradrenergic, but not D2 receptors, has been implicated in this effect. Disruption by the selective 5-HT2A agonist and hallucinogen, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI) is also preferentially blocked by atypical antipsychotics and the mechanism implicated is blockade of 5-HT2A receptors since a 5-HT2A antagonist but neither a 5-HT2C antagonist nor haloperidol effectively block DOI's effect on PPI (Geyer, Krebs-Thomson et al., 2001).

The neuropeptide neurotensin appears to inhibit dopamine function and produce preclinical effects similar to antipsychotics (Kinkead and Nemeroff, 2002) suggesting that neurotensin agonists may have potential as antipsychotic drugs. Supporting this notion, we have reported that PD149163, a modified neurotensin (8-13) analog (Lys(CH₂NH)Lys-Pro-Trp-tLe-Leu-OEt) (Wustrow et al., 1995) that crosses the blood brain barrier, antagonizes amphetamine-induced disruption of PPI after systemic administration (Feifel, Reza et al. 1999). In addition, we found that PD149163 antagonizes PPI deficits produced by the non-competitive NMDA antagonist dizocilpine (Feifel, Reza et al. 1999), suggesting that this compound modulates 5-HT2A and/or alpha-1 adrenergic transmission (Geyer, Krebs-Thomson et al., 2001). There is evidence that neurotensin regulates 5-HT brain systems (Heaulme, Leyris, et al., 1998) therefore, we hypothesized that PD149163 may produce antagonism of dizocilpine-

induced disruption of PPI by blockade of 5-HT_{2A} transmission. In order to test this hypothesis we investigated whether PD149163 could antagonize PPI disruption produced by DOI, a selective 5-HT_{2A} agonist.

METHODS

All experimental procedures were conducted in accordance with the University of California, San Diego guidelines for animal care and experimentation. Thirty-four male Sprague Dawley rats (250-300 grams at testing, Harlan Laboratories, San Diego) were housed under a 12h:12h light:dark schedule. On test days they were administered subcutaneous (SC) injections of 0 (saline), 0.01, 0.1, or 1 mg/kg of PD149163 (SRI International, Menlo Park, CA). Thirty minutes later they were injected SC with either saline or 0.5 mg/kg DOI (Sigma Chemicals, St. Louis, Mo). Animals were tested in startle chambers (San Diego Instruments, San Diego, CA) 20 minutes later. After one week, animals were tested a second time during which treatment and testing procedures were the same except that rats that received DOI on the first test day received saline on the second test day and vice versa. All testing occurred during the light phase of the rats' circadian illumination schedule.

Once placed in startle chambers each rats had a 5-minute acclimation period. A 65-dB background noise was continuously present throughout the session. The acclimation was followed by a 15-minute PPI test session during which rats were presented with 40-msec 120 dB startle pulses without a prepulse, or pulses preceded 100-msec by a prepulse of either 4, 8 or 12 dB above background. These four types of active

stimuli were presented in pseudorandom order along with no-sound trials with an average of 15 seconds separating them.

A startle response was recorded for all stimuli presentations. PPI for each animal was calculated as a percentage of the pulse-alone startle magnitude using the following formula: $[1 - (\text{startle magnitude after prepulse-pulse pair} / \text{startle magnitude after pulse only})] \times 100$. PPI data was analyzed using a repeated measures ANOVA with PD149163 dose as a between-subject factor and DOI treatment and prepulse intensity as within-subject factors. Significant effects were followed by post-hoc pair-wise comparisons of individual treatment groups using Bonferroni corrected t-tests.

RESULTS

There was no main effect of PD149163 but there was a significant main effect of DOI as it significantly disrupted PPI ($F[1,30] = 56.1, p \leq 0.001$). There was a significant main effect of prepulse intensity on percent PPI, reflected in more intense prepulses producing greater PPI ($F[2,60] = 80.3, p < 0.0001$). However, there was not a significant prepulse x DOI interaction, or prepulse x PD149163 interaction or prepulse x DOI x PD149163 interaction. **Therefore, the PPI data presented in the figure (main graph) is the mean of the PPI values produced by each of the individual prepulse intensities.** There was a significant DOI x PD149163 interaction ($F[3,30] = 7.3, p = .001$) and the data revealed that the highest dose of PD149163 reversed the DOI-induced disruption of PPI. **Compared to rats that did not receive DOI (saline), DOI treated rats had significantly decreased PPI in the group that did not receive PD149163 (saline) ($P < 0.01$) and in the groups that received 0.01 mg/kg**

($P < 0.001$) and 0.1 mg/kg ($P < 0.05$), but not 1 mg/kg PD149163. PPI exhibited by rats receiving DOI and 1 mg/kg PD149163 were significantly greater than PPI exhibited by rats receiving DOI and saline ($P < 0.01$).

There were no significant main or interaction effects of DOI or PD149163 on startle magnitude (Figure Insert).

DISCUSSION

To date, all drugs that have demonstrated a robust ability to antagonize DOI-induced disruption of PPI have been compounds with potent 5-HT_{2A} antagonism, including the atypical antipsychotic, risperidone and the selective 5-HT_{2A} antagonists, MDL100907 and ketanserin. In contrast, drugs that are not strong 5-HT_{2A} antagonists, including haloperidol, the selective D₂ antagonist raclopride, the 5-HT_{2C} antagonist, SDZ SER-082, and the beta-adrenergic /5-HT₁ receptor antagonist, propranolol, have failed to exhibit robust antagonism of DOI's effects on PPI (Geyer, Krebs-Thomson et al., 2001). In this respect, PD149163's ability to block DOI-induced disruption of PPI but not affect baseline PPI or startle magnitude supports our hypothesis that PD149163 may antagonize 5-HT_{2A} transmission.

The modulation of 5-HT systems by neurotensin has not been extensively studied, however neurotensin has been shown to stimulate the release of 5-HT in the brain (Heaulme, Leyris, et al., 1998). Neither neurotensin nor PD149163 is known to have a strong affinity for 5-HT_{2A} receptors. These compounds could alter 5-HT_{2A} transmission via activation of neurotensin receptors that, in turn, modulate

5-HT_{2A} transmission at the receptor level or further downstream. Evidence suggests that DOI-induced disruption of PPI is mediated by 5-HT_{2A} receptors in the ventral pallidum (Sipes and Geyer, 1997), a site where neurotensin receptors have been localized (Alexander and Leeman, 1997). The current evidence that PD149163 modulates 5-HT_{2A} transmission is notable since previous interest in neurotensin agonists as potential antipsychotics was based exclusively on evidence that they inhibited dopamine transmission. Inhibition of both 5-HT_{2A} and D₂ transmission is considered the pharmacological profile that distinguishes atypical antipsychotics from the more D₂ selective typical antipsychotics (Meltzer, 1999).

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Figure Caption:

The effect of PD149163 on PPI (main) and startle magnitude (insert) in rats receiving saline or DOI. **PPI data represents average of PPI produced by three different prepulse intensities.** * represents significantly lower ($P < 0.05$) than corresponding non-DOI treatment. + represent significantly greater ($P < 0.01$) than rats receiving 0 mg/kg dose of PD149163 and the same DOI treatment.

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PROPRIETARY INFORMATION

CASE No. 2003-091**TECHNOLOGY TRANSFER and INTELLECTUAL PROPERTY SERVICES, UCSD
INVENTION AND TECHNOLOGY DISCLOSURE FORM****A. TITLE OF INVENTION**

Create a short title describing the general nature of the invention without revealing the specific details that would enable others to reproduce the invention (e.g., new anticancer compound, method for chip fabrication, etc.). Please limit the title to 60 characters.

A method of screening for therapies for neuropsychiatric disorders using a Norway Rat Model

B. UCSD INVENTOR(S)

List all UCSD employees or students who intellectually contributed to the invention. Please also indicate any joint or special appointment with non-UCSD institutions (e.g., VA and HHMI) in the "Position" box.

Name: David Feifel	SS#: _____	Position: Assoc. Professor in Residence Joint or Non-UCSD Affiliation:
Dept.: Psychiatry Mail Code: MC8218	Work Address: 200 West Arbor Drive San Diego, CA 92130-8218	
Wk. Phone: (619) 543-2485	Fax: (619) 543-3738	Email: dfeifel@ucsd.edu
Hm. Address: 8241 La Jolla Scenic Drive North La Jolla, CA 92037		Hm. Phone (858) 558-6113

Name:	SS#: _____	Position: Lab Assistant Joint or Non-UCSD Affiliation:
Dept.: Mail Code:	Wk. Address:	
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Hm. Address:		Hm. Phone:

Name:	SS#: _____	Position: Post-Doc Fellow Joint or Non-UCSD Affiliation:
Dept.: Mail Code:	Wk. Address:	
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I. ABOUT THE INVENTION

Please write a summary of the invention following the numbered guidelines listed below. Since this information will be used to determine patentability, commercial uses, and potential licensees of the invention, please provide as many details as possible. If you have a written manuscript descriptive of your invention, please also attach a copy to this form.

1. What exactly does your invention do?

Represents a model which provides preclinical predictive information of whether a treatment is likely to be useful as psychotropic drug, particularly an antipsychotic.

2. What is unique, novel, or better about your invention as compared to existing art?

Can distinguish between typical (first generation) and "atypical" (newer generation) antipsychotic drugs.

Does not require manipulation (e.g. drug, surgical or environmental) of animals before examining test compound, as do existing in-vivo models.

Has stronger cross-species homology to humans.

Can provide comparative information about for a test compound regarding potency, speed of onset and duration of therapeutic-like effects.

3. What is the existing art to which you are comparing?

1. Existing in-vivo predictive models of antipsychotic effects (e.g. reversal of effects of social isolation, psychomimetic drugs, CNS lesions)
2. Existing ex-vivo predictive models of antipsychotic effects (e.g. affinity assays, electrophysiology, gene expression)

4. Describe how your invention works (or may work). Please include drawings, schematics, figures, etc., necessary to explain how the invention works or may work.

Brown Norway (BN) rats are administered a putative psychotropic treatment (e.g. several doses of a test drug) and then subsequently tested in startle chambers. Prepulse inhibition (PPI) of their startle reflex is measured. Normally BN rats have PPI levels that are low compared to other rat strains such as the Kyoto Wistar (the genetically closest animal). Treatments that fully or partially increase levels of PPI in BN rats to the levels of normal rats (e.g. Wistar Kyoto) have strong clinical potential as psychotropic drugs (e.g. antipsychotic potential).

5. Describe the stage of development of the invention (e.g., concept stage, experimental data stage, computer model simulation stage, working prototype stage, etc.). Please include data, photographs, etc., indicating the stages of development.

Conceptual with part experimental validation

6. What are potential commercial applications of your invention?

Screening new therapies for neuropsychiatric disorders.

CLAIMS

What is claimed is:

1. A model for providing preclinical predictive information concerning effectiveness of a treatment for neuropsychiatric disorders, comprising:
administering to a rat a particular therapy such as a pharmaceutical preparation containing a putative psychotropic drug or manipulation; and
measuring prepulse inhibition in a startle reflex response chamber wherein an increased prepulse inhibition level indicates a strong clinical potential as a psychotropic drug.
2. The model according to claim 1, wherein the rat is a Norway rat.
3. A method for screening new therapies for neuropsychiatric disorders, comprising:
administering to a rat a particular therapy such as a pharmaceutical preparation containing a putative psychotropic drug or manipulation; and
measuring prepulse inhibition in a startle reflex response chamber wherein an increased prepulse inhibition level indicates a potentially effective clinical treatment.
4. The method according to claim 3, wherein the rat is a Norway rat.
5. The method according to claim 3, wherein the neuropsychiatric disorder is schizophrenia.
6. The method according to claim 3, wherein the neuropsychiatric disorder is Huntington's Disease.
7. The method according to claim 3, wherein the neuropsychiatric disorder is bipolar disorder.

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